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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/904,766
Filing Date: July 12, 2001
Appellant(s): ASHKENAZI ET AL.

Panpan Gao
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 16 October 2007 appealing from the Office action mailed 01 November 2006.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The Appellant has correctly identified the related appeals, interferences, and judicial proceedings in the Appeal Brief of 16 October 2007.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

Pennica, D. et al. "WISP genes are members of the connective tissue growth factor family hat are up-regulated in Wnt-1-transformed cells and aberrantly expressed in human colon tumors" Proc. Natl. Acad. Sci., vol95 (December 1998, pp. 14717-14722.

Konopka, J.B. et al. "Variable expression of the translocated c-abl oncogene in Philadelphia-chromosome-positive B-lymphoid cell lines from chronic myelogenous leukemia patients" Proc. Natl. Acad. Sci. USA, vol83 (June 1986), pp. 4049-4052.

Godbout, R. et al. "Overexpression of a DEAD box protein (DDX1) in neuroblastoma and retinoblastoma cell lines" J. Biol. Chem. vol273, no. 33 (14 August 1998), pp. 21161-21168.

Bea, S. et al. "BMI-1 gene amplification and overexpression in hematological malignancies occur mainly in mantle cell lymphomas" Cancer Research vol61 (15 March 2001), pp. 2409-2412.

Li, R. et al. "Identification of putative oncogenes in lung adenocarcinoma by a comprehensive functional genomic approach" Oncogene vol25 (2006), pp. 2628-2635.

Sen "Aneuploidy and cancer" Curr. Opin. Oncol. vol12 (2000), pp. 82-88.

Hanna, J.S. and Mornin, D. "HER-2/neu Breast Cancer Predictive Testing" Pathology Associates Medical Laboratories (1999), pp. 1-2.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 44-46 and 49-52 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific, and substantial asserted utility or a well established utility.

The claims are directed to isolated polypeptides comprising the amino acid sequence set forth in SEQ ID NO: 96, with or without its associated signal sequence; polypeptides comprising the extracellular domain of the polypeptide set forth in SEQ ID NO: 96; and polypeptides comprising the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 209397. Dependent claims are directed to chimeric polypeptides comprising these sequences. The specification discloses the polypeptide of SEQ ID NO: 96, also known as PRO269, and indicates where the signal sequence and extracellular domain are located. The cDNA deposited as ATCC accession number 209397 is also disclosed. Appellants have gone on record as relying upon the gene amplification assay as providing utility and enablement for the claimed polypeptides. See Appeal Brief (received 16 October 2007), p. 5, second paragraph.

At pages 222-235 of the specification, Example 92 discloses a gene amplification assay in which genomic DNA encoding PRO269 had a ΔCt value of at least 1.0 for eight out of seventeen lung tumor samples when compared to a pooled control of blood DNA from several healthy volunteers. Example 92 asserts that gene amplification is associated with overexpression of the gene product (i.e., the polypeptide), indicating that the polypeptides are useful targets for therapeutic intervention in cancer and diagnostic determination of the presence of cancer (p. 222, lines 28-30).

First, there are several problems with the data provided in this example. PRO269 was reported as being amplified in less than half of the lung tumor samples tested. Therefore, if a new tumor lung sample were tested for PRO269 amplification, it is more likely than not that the PRO269 diagnostic test would yield a false negative result.

Second, the art recognizes that lung epithelium is can be aneuploid without the presence of cancer. Specifically, Sen (2000, Curr. Opin. Oncol. 12:82-88) teaches that cancerous tissue is known to be aneuploid, that is, having an abnormal number of chromosomes. A slight amplification of a gene does not necessarily correlate with overexpression in a cancer tissue, but can merely be an indication that the cancer tissue is aneuploid. The gene amplification assay in the instant specification does not provide a comparison between the lung tumor samples and normal lung epithelium and does not correct for aneuploidy. Thus it is not clear that PRO269 is amplified in cancerous lung epithelium more than in damaged (non-cancerous) lung epithelium. One skilled in the art would not conclude that PRO269 is a diagnostic probe for lung cancer unless it is clear that PRO269 is amplified to a clearly greater extent in true lung tumor tissue relative to non-cancerous lung epithelium.

Third, even if the data had been corrected for aneuploidy and a proper control had been used, the data have no bearing on the utility of the claimed PRO269 *polypeptides*. In order for PRO269 polypeptides to be overexpressed in tumors, amplified genomic DNA would have to correlate with increased mRNA levels and increased polypeptide levels. No data regarding PRO269 mRNA or PRO269

polypeptide levels in lung tumors have been brought forth on the record. The art discloses that a correlation between genomic DNA levels and mRNA levels cannot be presumed, nor can any correlation between genomic DNA levels and polypeptide levels. A specific example of the lack of correlation between genomic DNA amplification and increased mRNA expression is provided by Pennica et al. (1998, PNAS USA 95:14717-14722), who disclose that:

> "An analysis of *WISP*-1 gene amplification and expression in human colon tumors showed a correlation between DNA amplification and overexpression, whereas overexpression of *WISP*-3 RNA was seen in the absence of DNA amplification. In contrast, *WISP*-2 DNA was amplified in the colon tumors, but its mRNA expression was significantly reduced in the majority of tumors compared with the expression in normal colonic mucosa from the same patient."

See p. 14722, second paragraph of left column; pp. 14720-14721, "Amplification and Aberrant Expression of *WISPs* in Human Colon Tumors." Another specific example is provided by Konopka et al. (Proc. Natl. Acad. Sci. (1986) 83:4049-4052), who state that "Protein expression is not related to amplification of the abl gene but to variation in the level of bcr-abl mRNA produced from a single Ph1 template" (see abstract). Hanna and Mornin (1999, Pathology Associates Medical Laboratories) also supports the instant rejections. Hanna and Mornin provide another important example of a lack of correlation between gene amplification and mRNA/polypeptide overexpression, wherein diagnosis of breast cancer included testing both the amplification of the HER-2/neu gene as well as over-expression of the HER-2/neu gene product. Thus Hanna and Mornin provide evidence that the level of polypeptide expression must be tested

empirically to determine whether or not the polypeptide can be used as a diagnostic marker for a cancer. The specification does not provide data as to whether or not the polypeptide level of PRO269 was tested in normal and cancerous tissue, and thus the skilled artisan *must* perform additional experiments, as directed by the art. Since the asserted utility for the claimed antibodies is not in currently available form, and further experimentation is *required* to reasonably confirm the asserted real-world use, the asserted utility is not substantial.

The *general* concept of gene amplification's lack of correlation with mRNA/polypeptide overexpression in cancer tissue is addressed by Godbout et al. (1998, J. Biol. Chem. 273(33):21161-8), who teach a general lack of correlation between gene amplification and mRNA/polypeptide overexpression. The abstract of Godbout et al. teaches "The DEAD box gene, DDX1, is a putative RNA helicase that is co-amplified with MYCN in a subset of retinoblastoma (RB) and neuroblastoma (NB) tumors and cell lines. ***Although gene amplification usually involves hundreds to thousands of kilobase pairs of DNA, a number of studies suggest that co-amplified genes are only overexpressed if they provide a selective advantage to the cells in which they are amplified.***" (emphasis added). The polypeptide encoded by the DDX gene *had been characterized* as being a putative RNA helicase, a type of enzyme that *would be expected to confer a selective advantage* to the cells in which it (the DDX gene) was amplified. On page 21167, right column, first full paragraph, Godbout et al. state ***"It is generally accepted that co-amplified genes are not over-expressed unless they provide a selective growth advantage to the cell*** (48, 49).

For example, although ERBA is closely linked to ERBB2 in breast cancer and both genes are commonly amplified in these tumors, ERBA is not overexpressed (48). Similarly, three genes mapping to 12q13-14 (CDK4, SAS and MDM2) are overexpressed in a high percentage of malignant gliomas showing amplification of this chromosomal region, while other genes mapping to this region (GADD153, GL1, and A2MR) are rarely overexpressed in gene-amplified malignant gliomas (50, 51). The first three genes are probably the main targets of the amplification process, while the latter three genes are probably incidentally included in the amplicons." (emphasis added). There is no evidence in the instant application that PRO269 confers any growth advantage to a cell, and thus it cannot be presumed that the PRO269 polypeptide is overexpressed because the genomic DNA including the gene being studied is amplified.

An additional reference that provides evidence that gene amplification does not generally lead to increased transcript is Li et al. (2006, Oncogene, Vol. 25, pages 2628-2635). Li et al. used a functional approach that integrated simultaneous genomic and transcript microarray, proteomics, and tissue microarray analyses to directly identify putative oncogenes in lung adenocarcinoma. On page 2633, right column, Li et al. state: "***In our study, 68.8% of the genes showing over-representation in the genome did not show elevated transcript levels***, implying that at least some of these genes are 'passenger' genes that are concurrently amplified because of their location with respect to amplicons but *lack biological relevance in terms of the development of lung adenocarcinoma.*" Since more than half of the amplified genes were not overexpressed, Li et al. constitutes strong evidence that ***it is more likely than not that***

gene amplification does NOT correlate with increased protein levels, absent evidence that the polypeptide has biological relevance in cancer. There is no such evidence for PRO269.

Therefore, data pertaining to PRO269 genomic DNA do not indicate anything significant regarding the claimed PRO269 polypeptides. The data do not support the specification's assertion that PRO269 polypeptides can be used as cancer diagnostic agents. Significant further research would have been required of the skilled artisan to reasonably confirm that the PRO269 polypeptide is overexpressed in any cancer to the extent that the polypeptide could be used as a cancer diagnostic agent, and thus the asserted utility is not substantial. In the absence of information regarding whether or not PRO269 polypeptide levels are also different between specific cancerous and normal tissues, the proposed use of the PRO269 **polypeptides** as diagnostic markers and therapeutic targets are simply starting points for further research and investigation into potential practical uses of the polypeptides and antibodies. See Brenner v. Manson, 148 U.S.P.Q. 689 (Sup. Ct., 1966), wherein the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an Appellant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

In view of the preponderance of evidence supporting the rejection (Pennica et al., Konopka et al., Sen, Godbout et al., and Li et al., the rejection is properly maintained.

Claims 44-46 and 49-52 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible, specific, and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

(10) Response to Argument

At p. 4 of the Brief, Appellants acknowledge that the examiner "has withdrawn the rejections" based on several references, and that several references relied upon by Appellants would no longer be addressed. In the interest of clarifying this for the Board, it is noted that the rejections were not withdrawn. Rather, the original version of the rejections relied upon three main issues: 1) whether genomic DNA levels were predictive of mRNA levels; 2) whether genomic DNA levels were predictive of polypeptide levels; and 3) whether mRNA levels were predictive of polypeptide levels. Many references were relied upon by both Appellants and the examiner to support their differing positions on these three issues. Over the course of prosecution, the examiner indicated that the preponderance of the evidence no longer supported her position with regard to issue 3), and thus the references relied upon by the examiner and Appellants regarding issue 3) would no longer be addressed. However, the rejections themselves were not withdrawn. Please see p. 2 of the advisory action of 30 May 2007 for a complete explanation.

At pp. 4-5 of the Brief, Appellants explain the difference between the gene amplification assay and the microarray assay. Appellants point to a recent Board decision reversing the examiner in a microarray case. Appellants quote the decision that "there is a strong correlation between mRNA levels and protein expression, and the Examiner has not presented any evidence specific to the PRO1866 polypeptide to refute that." Appellants urge that there is a similar situation in the instant application wherein the Examiner has not presented any evidence specific to the PRO269 polypeptide to refute Appellant's assertion of a correlation between DNA levels and mRNA/polypeptide levels. This has been fully considered but is not found to be persuasive. The fact pattern in the case at issue in the Board decision differs significantly from the fact pattern in the instant case. In the microarray case decided by the Board, there were several critical pieces of evidence supporting Appellant's position in addition to the assertion in the specification that increased mRNA levels correlated with increased polypeptide levels. In particular, there were multiple declarations submitted under 37 C.F.R. § 1.132, including highly probative declarations containing further data. In the instant case, the preponderance of the evidence does not support the assertion in the specification that increased genomic DNA levels correlate with increased polypeptide levels. Indeed, the Ashkenazi declaration filed under 37 C.F.R. 1.132 on 21 May 2004 actually supports the Examiner's position. Based on the preponderance of the evidence as a whole (which is discussed in detail below), the rejections are being maintained.

At p. 5 of the Brief, Appellants review the gene amplification data disclosed in the specification, and refer to the Goddard declaration submitted under 37 C.F.R. 1.132 on 21 February 2003 as supporting the assertion that the gene is a useful marker for diagnosis of lung cancer. This has been fully considered but is not found to be persuasive as it is off-point. Specifically, the claims are directed to PRO269 *polypeptides*, not PRO 269 *genes*.

At pp. 5-6 of the Brief, Appellants argue that ample evidence has been submitted to show that, in general, if a gene is amplified in cancer, it is more likely than not that the encoded polypeptide is expressed at an elevated level. Appellants briefly point to Orntoft et al., Hyman et al., Pollack et al., and the two Polakis declarations filed under 37 C.F.R. § 1.132. Finally, Appellants assert that even if a polypeptide encoded by an amplified gene were not overexpressed, it would still have a specific, substantial and credible utility as tools for more accurate tumor classification. Appellants briefly point to the Ashkenazi declaration submitted under 37 C.F.R. § 1.132 and the Hanna and Mornin reference as supporting their position. This has been fully considered but is not found to be persuasive. Orntoft et al. could only compare the levels of about 40 well-resolved and focused *abundant* proteins." (See abstract). It would appear that Appellants have provided no fact or evidence concerning a correlation between the specification's disclosure of *low* levels of amplification of DNA (which were not characterized on the basis of those in the Orntoft publication) and an associated rise in level of the encoded polypeptide. Hyman et al. found 44% of *highly* amplified genes showed overexpression at the mRNA level, and 10.5% of *highly* overexpressed genes

were amplified; thus, even at the level of high amplification and high overexpression, the two do not correlate. Further, the article at page 6244 states that of the 12,000 transcripts analyzed, a set of 270 was identified in which overexpression was attributable to gene amplification. This proportion is approximately 2%; the Examiner maintains that 2% does not provide a reasonable expectation that the slight amplification of PRO269 would be correlated with elevated levels of mRNA, much less polypeptide. Hyman et al. do not examine polypeptide expression. Pollack et al. is similarly limited to highly amplified genes which were not evaluated by the method of the instant specification. None of the three references are directed to gene amplification, mRNA levels, or polypeptide levels in lung cancer. The two Polakis declarations are limited to the issue of whether or not mRNA levels are predictive of polypeptide levels, which is no longer an issue in this rejection. Finally, the Ashkenazi declaration and the Hanna and Mornin reference support the Examiner's position in that they provide further evidence that gene amplification does not correlate with increased mRNA/polypeptide levels. It is noted that nowhere in the specification is it asserted that tumors could be more accurately classified if the genomic DNA is amplified and the polypeptide is not overexpressed.

At p. 6, second paragraph, of the Brief, Appellants argues that the sale of gene expression chips constitutes evidence that the research community believes that the information obtained from these chips is useful in that it is more likely than not that the information is informative of polypeptide levels. This has been fully considered but is not found to be persuasive for two reasons. First, evidence of commercial success,

while probative as a secondary consideration of non-obviousness, has no bearing on the legal issue of utility and enablement. Second, gene chips speak to the issue of whether mRNA levels are predictive of polypeptide levels, which is no longer relevant to the instant rejections.

At p. 6, third paragraph, to p. 7, second paragraph, Appellants argue that the Sen reference supports Appellants' position that the PRO269 is a marker for cancer or precancerous cells or damaged tissue, and thus the PRO269 gene finds utility as a diagnostic for cancer or individuals at risk for cancer. Appellants also provide a general summary. This has been fully considered but is not found to be persuasive. The application as originally filed never asserts that the PRO269 gene or polypeptide is useful to diagnose individuals *at risk for* cancer. Rather, the specification states at p. 222, lines 28-30, that, "Amplification is associated with overexpression of the gene product; indicating that the polypeptides are useful targets for therapeutic intervention in certain cancers such as colon, lung, breast and other cancers and diagnostic determination of the presence of those cancers." Thus, Appellants' arguments contradict the assertion in the specification, and support the instant rejections.

Appellants' detailed arguments begin at p. 7 of the appeal brief. Appellant begins with a review of the legal standard for utility, with which the examiner takes no issue.

Beginning at p. 10 of the Brief, Appellants review Example 92, and refer to the Goddard declaration as establishing that an amplification of at least 2-fold is significant and indicative of a cancer diagnostic marker. The Goddard declaration under 37

CFR 1.132 filed 21 February 2003 is insufficient to overcome the rejection of claims 44-46 and 49-52 based upon 35 U.S.C. §§ 101 and 112, first paragraph, as set forth in the last Office action for the following reasons. In assessing the weight to be given expert testimony, the examiner may properly consider, among other things, the nature of the fact sought to be established, the strength of any opposing evidence, the interest of the expert in the outcome of the case, and the presence or absence of factual support for the expert's opinion. See Ex parte Simpson, 61 USPQ2d 1009 (BPAI 2001), Cf. Redac Int'l. Ltd. v. Lotus Development Corp., 81 F.3d 1576, 38 USPQ2d 1665 (Fed. Cir. 1996), Paragon Podiatry Lab., Inc. v. KLM Lab., Inc., 948 F.2d 1182, 25 USPQ2d 1561, (Fed. Cir. 1993). In the instant situation, the nature of the fact sought to be established is whether or not a 2 fold to 3.5 fold amplification in eight out of seventeen lung tumor samples is significant, and whether such data have any relevance to the claimed subject matter, i.e., PRO269 polypeptides. The significance can be questioned based on the strength of opposing evidence. In the instant case, the controls used were not matched, non-tumor lung samples but rather was a pooled DNA sample from blood of healthy subjects. The art uses matched tissue samples (see Pennica et al., Konopka et al.). This art, as well as the Sen, Godbout et al., and Li et al. references cited above, constitute strong opposing evidence as to whether or not the claimed polypeptides have utility and enablement based on a presumption of polypeptide overexpression in view of gene amplification data. Finally, while the Goddard declaration speaks to the utility and enablement of genes, it does not speak to whether or not the encoded polypeptides are

also found at increased levels in cancerous tissues. Since the claims under examination are directed to polypeptides, not genes, this question is critical.

At pp. 11-12 of the Brief, Appellants argue that ample evidence has been provided (Orntoft et al., Hyman et al., Pollack et al., over 100 references, Polakis I and II declarations, Ashkenazi declaration) that it is more likely than not that, if a gene is amplified in cancer, the encoded polypeptide is also expressed at an elevated level. This has been fully considered but is not found to be persuasive. Orntoft et al., Hyman et al., and Pollack et al. are flawed as discussed at pp. 11-12 above. The "over 100 references" referred to by Appellant is listed in the IDS of 22 August 2006. Virtually none of these references address the issue of whether or not gene amplification correlates with increased mRNA/polypeptide levels. The relevant references have been addressed fully on the record, including in the instant examiner's answer. The Polakis I and II declarations are limited to the issue of whether or not mRNA levels are predictive of polypeptide levels, which is no longer an issue in this rejection. Finally, the Ashkenazi declaration supports the Examiner's position in that it provides further evidence that gene amplification does not correlate with increased mRNA/polypeptide levels.

Beginning at p. 12 of the Brief, Appellants again urge that the PRO269 gene amplification is significant and it is more likely than not that an increase in genomic DNA copy number correlates with an increase in polypeptide levels. At pp. 12-13, Appellants criticize Pennica et al. and Konopka et al. as not being specific to PRO269, instead as being specific to other genes, and not establishing a general trend. Appellants urge that

there is no legal requirement for accurate prediction. This has been fully considered but is not found to be persuasive. The instant application also presents data from a single gene at a time and makes conclusions about gene products from genomic DNA data. Pennica et al. and Konopka et al. constitute evidence that it cannot be assumed that amplified genomic DNA results in overexpressed gene product. Godbout et al. and Li et al. also provide evidence to this effect with respect to the general concept of whether or not gene amplification correlates with increased mRNA/polypeptide expression. Finally, Sen constitutes evidence that, in general, non-cancerous epithelial tissues are frequently aneuploid, and thus an increase in genomic DNA is not diagnostic of cancer. Beginning at p. 13, Appellants discuss the Godbout et al. and Bea et al. references. Appellants urge that the two references were cited as evidence that gene amplification correlates well with polypeptide expression levels. Appellants urge that the passage quoted by the Examiner from Godbout et al. relies on two references from 1987 and 1992, whereas the references relied upon by Appellants are more recent, such as 2002. Finally, Appellants argue that Bea et al. supports Appellant's position that gene amplification is correlated with both increased mRNA and protein expression. This has been fully considered but is not found to be persuasive. It is noted that the instant application claims priority to 1997, and thus the references of 1987 and 1992 are not completely out of date. Furthermore, Godbout et al. was published in 1998 and fully relies on the cited publications as being reflective of the state of the art. Also, the publications from 2002 are not reflective of the state of the art at the time of the invention, which was sometime before 1997. Finally, Godbout et al. make a strong case

in favor of the rejection. Specifically, Godbout et al. state, "*It is generally accepted that co-amplified genes are not over-expressed unless they provide a selective growth advantage to the cell.*" There is no evidence or assertion of record that PRO269 provides a selective growth advantage to a cell, and thus it cannot be presumed that the polypeptide is overexpressed because the genomic DNA including the gene being studied is amplified. Regarding Bea et al., it is not unexpected that a putative oncogene that seems to participate in cell cycle regulation and senescence, when amplified in the genome, would also be amplified as mRNA and have correspondingly increased polypeptide expression. PRO269 is not a putative oncogene, and the function of the encoded polypeptide is not known. Godbout et al. and Bea et al. clearly point out that whether or not a polypeptide is over-expressed depends strictly upon the function of the polypeptide. The instant specification has not established that over-expression of PRO269 polypeptide provides a growth advantage to a cell, and thus it cannot be said that Bea et al. and Godbout et al. constitute evidence to support Appellants' position. In fact, Godbout et al. and Bea et al. support the instant rejection.

At pp. 14-15 of the Brief, Appellants argue that Orntoft et al. show a highly significant correlation between mRNA and protein alterations. This has been fully considered but is not found to be persuasive. Again, the issue of whether or not mRNA levels are predictive of polypeptide levels is no longer considered relevant to the instant rejections. The remaining issues are whether or not gene amplification correlates with increased mRNA/polypeptide levels. On this, Orntoft et al. does not clearly support Appellants' position. Specifically, Orntoft et al. appear to have looked at increased DNA

content over large regions of chromosomes and compare that to mRNA and polypeptide levels from the chromosomal region. Their approach to investigating gene copy number was termed CGH. Orntoft et al. do not appear to look at gene amplification, mRNA levels and polypeptide levels from a single gene at a time as was done in the instant application. Orntoft et al. concentrated on regions of chromosomes with strong gains of chromosomal material containing clusters of genes (pg 40). This analysis was not done for PRO269 in the instant specification. That is, it is not clear whether or not PRO269 is in a gene cluster in a region of a chromosome that is highly amplified.

At pp. 15-16, Appellants address the Wildsmith et al. reference. However, since this reference is limited to the issue of whether or not mRNA levels are predictive of polypeptide levels, the Examiner no longer relies on Wildsmith et al. as supporting the instant rejections.

At pp. 16-17, Appellants discuss the Li et al. reference. Appellants urge that Li et al. acknowledge that their results differed from those of Hyman et al. and Pollack et al., and note that the difference may be due to different methodologies. Appellants refer to the supplemental information accompanying the Li et al. article, enclosed as Exhibit A. Appellants urge that Li et al. used an amplification copy ratio of only 1.4, which is not significant according to the Goddard declaration, and that a copy number of at least 2 was necessary. This has been fully considered but is not found to be persuasive. First, it is noted that Hyman et al. also found that less than half of the amplified genes were overexpressed at the mRNA level, even though they only investigated genes in genomic DNA regions that were amplified at least 2-fold (argued in more detail above).

Furthermore, Li et al. did not limit their studies to genes that were amplified at less than 2-fold. In fact, the supplemental information indicates that some of the samples were required to bind with a probe requiring at least 2-fold amplification:

> Genes with copy number ratio > 1.40 (representing the upper 5% of the CGH ratios across all experiments) were considered to be overrepresented. A genomic fragment that contained six or more adjacent probes showing a copy number ratio > 1.40, or a region with at least three adjacent probes with a copy number ratio > 1.40 **and no less than one probe with a ratio > 2.0**, were considered to be amplicons. (emphasis added, from 1st page of supplemental material)

At pp. 17-18 of the Brief, Appellants argue that Sen supports Appellants' position, in that there is utility for an aneuploid gene at least as a marker for cancer or precancerous cells or damaged tissue. Appellants urge that Sen constitutes evidence of the utility for genetic biomarkers in epithelial tissues at cancer risk. This has been fully considered but is not found to be persuasive. The application never asserts a utility for PRO269 genes or polypeptides as biomarkers for cancer *risk*. Rather, the specification states at p. 222, lines 28-30, that, "Amplification is associated with overexpression of the gene product, indicating that the polypeptides are useful targets for therapeutic intervention in certain cancers such as colon, lung, breast and other cancers and diagnostic determination of the presence of those cancers." It also cannot be established that utility as a biomarker for cancer risk is a well-established utility. One skilled in the art cannot look at the structure of a new polypeptide and conclude that it is such a biomarker without testing it. Thus, Appellants' arguments contradict the assertion in the specification, and support the instant rejections.

Beginning at p. 18, Appellants point to the Polakis declarations as evidence that mRNA levels correlate with polypeptide levels. This has been fully considered but is not

found to be persuasive. The Polakis I and II declarations under 37 CFR 1.132 filed 03 November 2004 and 30 March 2006, respectively, are insufficient to overcome the rejection of claims 44-46 and 49-52 based upon 35 U.S.C. §§ 101 and 112, first paragraph, as set forth in the last Office action because they are limited to an issue that is no longer relevant (i.e., whether or not mRNA levels are predictive of polypeptide levels). The instant rejections are primarily based on whether or not genomic DNA levels (as measured by the gene amplification assay) correlate with either mRNA levels or polypeptide levels. The preponderance of the totality of the evidence indicates that genomic DNA levels are not predictive of mRNA or polypeptide levels.

At p. 19 of the Brief, Appellants argue that the sale of gene expression chips constitutes evidence that the research community believes that the information obtained from these chips is useful in that it is more likely than not that the information is informative of polypeptide levels. This has been fully considered but is not found to be persuasive for two reasons. First, evidence of commercial success, while probative as a secondary consideration of non-obviousness, has no bearing on the legal issue of utility and enablement. Second, gene chips speak to the issue of whether mRNA levels are predictive of polypeptide levels, which is no longer relevant to the instant rejections.

At pp. 19-20 of the Brief, Appellants conclude that, based on the asserted utility for PRO269 in the diagnosis of selected lung tumors, the reduction to practice of the PRO269 polypeptide sequence, the disclosure of methods for making PRO269 polypeptides and chimeric polypeptide comprising the same, and example 92 regarding the gene amplification assay, one skilled in the art would know exactly how to make and

use the claimed antibodies for diagnosis of lung cancer without undue experimentation. Appellant concludes that the utility of the claimed PRO269 antibodies has been achieved. This has been fully considered but is not found to be persuasive for the following reasons. Regarding the gene amplification assay itself, it is noted that the assay did not correct for aneuploidy, which is a common feature of non-cancerous, damaged lung epithelium (evidenced by Sen). The specification does not assert a utility for PRO269 as a biomarker for damaged, pre-cancerous tissue, and such is not a well-established utility. Gene amplification publications used matched tissue controls, unlike Appellants (Pennica et al., Konopka et al., Godbout et al., Li et al.). Contrary to Appellants' assertion, the state of the art indicates that gene amplification is not generally associated with overexpression of the encoded gene product, as evidenced by Sen, Pennica et al., Konopka et al., Godbout et al., Hyman et al., and Li et al. Finally, a declaration setting forth the expert opinion of Dr. Ashkenazi (received 21 May 2004) contradicts the assertion of utility in the specification, wherein the specification indicates that gene amplification is associated with protein overexpression but Dr. Ashkenazi indicates that this is not always the case. This is also stated several times by Appellants in the Appeal Brief of 16 October 2007. Since significant further research would have been required of the skilled artisan to reasonably confirm that the claimed PRO269 polypeptides are overexpressed in any cancer to the extent that they could be used as cancer diagnostic agents, the asserted utility is not substantial. In the absence of information regarding whether or not PRO269 polypeptide levels are also different between specific cancerous and normal tissues, the proposed use of the PRO269

polypeptides as diagnostic markers and therapeutic targets are simply starting points for further research and investigation into potential practical uses of the polypeptides. See Brenner v. Manson, 148 U.S.P.Q. 689 (Sup. Ct., 1966), wherein the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an Appellant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

Hanna and Mornin (1999, Pathology Associates Medical Laboratories) also supports the instant rejections. Hanna and Mornin provide another important example of a lack of correlation between gene amplification and mRNA/polypeptide overexpression, wherein diagnosis of breast cancer included testing both the amplification of the HER-2/neu gene as well as over-expression of the HER-2/neu gene product. Thus Hanna and Mornin provide evidence that the level of polypeptide expression must be tested empirically to determine whether or not the polypeptide can be used as a diagnostic marker for a cancer. The specification does not provide data as to whether or not the polypeptide level of PRO269 was tested in normal and cancerous tissue, and thus the skilled artisan *must* perform additional experiments, as directed by the art. Since the asserted utility for the claimed antibodies is not in currently available form, and further experimentation is *required* to reasonably confirm the asserted real-world use, the asserted utility is not substantial.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

(12) Oral Hearing

It does not appear that Appellant has requested an oral hearing at this time. However, if an oral hearing is requested, the examiner requests the opportunity to present arguments at the hearing.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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